REMARKS

Claims 97, 102, 104, 105, 110, 111, 114, 115, 119, 121-123, 126, 128, 129, 131-133, 135, 149-156, 158, 167, 168, 170, 172, 174, and 176 have been amended. Claims 116 and 130 have been cancelled without prejudice or disclaimer. Claims 27, 49, 64, 67, 68, 71-74, 76, 77, 79, 81-86, 89-91, 94, 96, 97, 102, 104, 105, 110, 111, 114, 115, 119, 121-123, 126, 128, 129, 131-135, 138, 139, 144-168, 170, 172, and 174-178 are pending in the instant application. Support for the amendments to the claims can be found in the specification at, for example, page 25, lines 3-6. The objections and rejections set forth in the Office Action have been overcome by amendment or are traversed by argument below.

1. Rejection of claims 97, 102, 104, 168, 170, and 172 under 35 U.S.C. § 101

The Office Action asserts a rejection of claims 97, 102, 104, 168, 170, and 172 under 35 U.S.C. § 101. The Action states that claims 97, 102, 104, 168, 170, and 172 are directed to a broad genus of host cells comprising a vector that comprises a claimed nucleic acid molecule. The Action also states that the specification contemplates human host cells *in vivo*, and therefore, contemplates transgenic humans. The Action therefore asserts that claims 97, 102, 104, 168, 170, and 172 are directed to non-statutory subject matter.

Applicants have amended claims 97, 102, and 104 to recite "[a] cultured host cell," thereby overcoming the rejection with regard to these claims. Support for this amendment can be found in the specification at page 25, lines 3-6 (*see* substitute specification filed January 7, 2002), which states that preferred eukaryotic hosts include mammalian cells ***either*** *in vivo* or in tissue culture. In addition, because claims 168, 170, and 172 recite a process of producing a recombinant polypeptide comprising ***culturing*** a host cell, Applicants respectfully disagree with the Action's assertion that the "recombinant host cells" of claims 168, 170, and 172 encompass transgenic humans. Nevertheless, in order to expedite prosecution, and in Applicants' view because it will have no substantive effect on the proper scope of the pending claims, Applicants have amended claims 168, 170, and 172 to recite "a host cell." Withdrawal of this rejection is therefore respectfully solicited.

2. Rejections of claims 116, 199, and 130 under 35 U.S.C. § 112, second paragraph

The Office Action asserts a rejection of claims 116, 119, and 130 under 35 U.S.C. § 112,

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second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. The Action states that claims 116 and 119 are indefinite because there is insufficient antecedent basis for the phrase "the prokaryotic cell."

Applicants have cancelled claim 116 and have amended claim 119 to recite "[t]he process of Claim 176, wherein the eukaryotic cell is a yeast cell." Applicants, therefore, respectfully request that this ground of rejection be withdrawn.

The Action also states that claim 130 is indefinite because it recites a host cell containing a heterologous promoter operationally linked to a nucleic acid molecule encoding the amino acid sequence of SEQ ID NO: 2, but depends from claim 104, which depends from claim 67, which recites an isolated nucleic acid molecule encoding a polypeptide having the ability to bind TNF, wherein said polypeptide consists of the amino acid sequence of SEQ ID NO: 4, wherein the amino acid sequence of SEQ ID NO: 4 is smaller than the amino acid sequence of SEQ ID NO: 2.

Applicants have cancelled claim 130, rendering this rejection moot.

Applicants respectfully contend that rejections based on 35 U.S.C. § 112, second paragraph, have been overcome by amendment or traversed by argument, and request that the Examiner withdraw all rejections made on this basis.

3. Rejections of claims 97, 102, 104, 168, 170, and 172 under 35 U.S.C. § 112, first paragraph

The Office Action asserts a rejection of claims 97, 102, 104, 168, 170, and 172 under 35 U.S.C. § 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most clearly connected, to use the invention. The Action states that because the specification contemplates mammalian host cells *in vivo*, it is implied that the specification contemplates three subgenera in which such host cells can be made and used: (i) in culture, (ii) in gene therapy, and (iii) in multicellular, transgenic organisms. The Action also states that while the use of host cells in culture is enabled, the use of host cells in gene therapy or in multicellular, transgenic organisms is not enabled. In particular, the Action states that because of the large quantity of experimentation required to generate a transgenic animal expressing the disclosed protein or to introduce and express the claimed nucleic acid in the cell of an organism for therapeutic purposes; the absence of working

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examples directed to the above; the complex nature of the invention; the state of the prior art which establishes the unpredictability of making transgenic animals and the unpredictability of gene therapy; and the breadth of the claims, which fail to recite any cell type limitations, the skilled artisan would have to exercise undue experimentation in order to make and use the full scope of the claimed invention. The Action suggests that this rejection could be overcome by amending the claims to recite "[a]n isolated host cell," because such an amendment would clarify that the claims are directed only to host cells which are to be made and used in culture.

As described in section 1 above, Applicants have amended claims 97, 102, and 104 to recite "[a] cultured host cell," thereby overcoming this rejection with regard to these claims. Because claims 168, 170, and 172 recite a process of producing a recombinant polypeptide comprising ***culturing*** a host cell, Applicants respectfully disagree with the Action's assertion that claims 168, 170, and 172 encompass transgenic humans or gene therapy. Nevertheless, in order to expedite prosecution, and in Applicants' view because it will have no substantive effect on the proper scope of the pending claims, Applicants have amended claims 168, 170, and 172 to recite "a host cell." Withdrawal of this rejection is therefore respectfully solicited.

4. Claim of priority

The Office Action asserts that the amino acid sequence set forth in SEQ ID NO: 4 is entitled under 35 U.S.C. § 119(a) to the benefit of the June 21, 1989 filing date of German Patent Application No. P39 20 282.8, but not to the April 21, 1989 filing date of German Patent Application No. P39 13 101.7.

Although Applicants respectfully disagree with the Action's priority determination, Applicants contend that this determination is not relevant to the rejections made in the instant Action. Applicants, therefore, acknowledge the Action's priority determination, and elect to address this determination when it becomes relevant to the patentability of the instant claims.

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5. Rejection of claims 27, 49, 64, 67, 68, 71-74, 76, 77, 79, 81-86, 89-91, 94, 96, 97, 102, 104, 105, 110, 111, 114-116, 119, 121-123, 126, 128-135, 138, 139, 144-168, 170, 172, and 174-178 under 35 U.S.C. § 102

The Office Action asserts a rejection of claims 27, 49, 64, 67, 68, 71-74, 76, 77, 79, 81-86, 89-91, 94, 96, 97, 102, 104, 105, 110, 111, 114-116, 119, 121-123, 126, 128-135, 138, 139, 144-168, 170, 172, and 174-178 under 35 U.S.C. § 102(e) as being anticipated by U.S. Patent No. 5,695,953 (the '953 patent), which the Action asserts has an effective priority date of September 12, 1988. In particular, the Action states that the '953 patent discloses a soluble TNF inhibitory protein having an amino terminal sequence that is the same as the amino terminal sequence of the protein of SEQ ID NO: 4 of the instant application. The Action also states that subsequent U.S. Patent No. 5,811,261 indicates that the TNF inhibitory protein disclosed in the '953 patent is identical to the protein of SEQ ID NO: 2 of the instant application, and that the TNF inhibitory protein disclosed in the '953 patent is encoded by a nucleic acid that is identical to the coding portion of SEQ ID NO: 1 of the instant application.

To support a rejection under 35 U.S.C. § 102, "the four corners of a single, prior art document [must] describe every element of the claimed invention, either expressly or inherently, such that a person of ordinary skill in the art could practice the invention without undue experimentation." *In re Paulsen*, 30 F.3d 1475, 1479 (Fed. Cir. 1994). The exclusion of even a single claimed element from a reference, no matter how insubstantial or obvious, is enough to negate anticipation. *Connell v. Sears, Roebuck & Co.*, 220 U.S.P.Q. (BNA) 193, 198 (Fed. Cir. 1983). The identical invention must also be shown in the single prior art reference in as complete detail as contained in the application against which the reference is cited. *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236 (Fed. Cir. 1989). Moreover, the disclosure in an assertedly anticipating reference must provide an enabling disclosure of the desired subject matter; mere naming or description of the subject matter is insufficient, if it cannot be produced without undue experimentation. M.P.E.P § 2121.01; *Elan Pharm., Inc. v. Mayo Found. for Med. Educ. & Research*, 346 F.3d 1051, 1054 (Fed. Cir. 2003); *Amgen, Inc. v. Hoechst Marion Roussel, Inc.*, 126 F. Supp. 2d 69, 88 (D. Mass 2001) (citing *Akzo N.V. v. United States Int'l Trade Comm'n*, 808 F.2d 1471, 1479 (Fed. Cir. 1986)). A reference contains an "enabling disclosure" if the public was in possession of the claimed invention before the date of invention. M.P.E.P § 2121.01. "Such

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possession is effected if one of ordinary skill in the art could have combined the publication's description of the invention with his [or her] own knowledge to make the claimed invention." *In re Donohue*, 766 F.2d 531 (Fed. Cir. 1985).

Applicants respectfully disagree with the Action's assertion that the '953 patent, which provides only a ***partial, incomplete*** amino acid sequence of a TNF inhibitory protein – and ***no nucleotide sequence whatsoever*** (*see* col. 4, ln. 27- 31; col. 10, ln. 43-46; and col. 12, ln. 32-37), anticipates the claimed invention. In fact, because the '953 patent does not disclose ***any*** information about the nucleotide sequence of TNF binding protein (TNF-BP) – and discloses ***only*** fourteen of the first sixteen amino acid residues of a TNF-BP, the '953 patent provides no details about the claimed invention – let alone describe the claimed invention in as complete detail as does the instant application. Moreover, because the '953 patent did not place the claimed invention into the public's possession, and a skilled artisan could not have combined the disclosure of the '953 patent with her own knowledge to make the claimed invention, the '953 patent does not contain an enabling disclosure with respect the instantly claimed invention.

In noting that subsequent U.S. Patent No. 5,811,261 indicates that the TNF inhibitory protein disclosed in the '953 patent is identical to the protein of SEQ ID NO: 2 of the instant application, and that the TNF inhibitory protein disclosed in the '953 patent is encoded by a nucleic acid that is identical to the coding portion of SEQ ID NO: 1 of the instant application, the Action appears to suggest that the purified TNF inhibitory protein of the '953 patent inherently anticipates the claimed invention. However, even if the '953 patent disclosed the nucleotide sequence of its purified TNF-BP preparation – which it does not, the evidence clearly indicates that the '953 patent would not have disclosed an isolated nucleic acid molecule encoding a polypeptide comprising (or consisting of) the amino acid sequence as set forth in SEQ ID NO: 4. Instead, because the human urinary TNF-BP disclosed in the '953 patent does ***not*** constitute a single species as a result of the processing of the N-terminus of human urinary TNF *in vivo*, any nucleic acid molecule composition derived from the '953 patent's purified TNF-BP preparation would comprise multiple species. In contrast, the nucleic acid molecules of the instantly claimed invention encode a polypeptide constituting a single species.

In particular, the evidence indicates that the purification protocols described in the '953 patent and those described by Applicants are substantially similar, and that Applicants obtained a heterogeneous mixture of TNF-BP proteins from human urine. With regard to the teachings of the

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instant specification, Applicants subjected highly purified samples of human urinary TNF-BP to SDS-PAGE, which "resulted in a diffuse band" (page 38, lines 8-9). The specification confirms that the "diffused appearance of the band" was "due to the presence of . . . a second polypeptide in a smaller amount" (page 38, lines 11-13). The second polypeptide "is longer than TNF-BP at the end terminus" and its sequence "coincides with the N-terminal secondary sequence . . . which is obviously split off from the processed protein" (page 38, lines 15-16, 19-20). Amino acid sequence analysis revealed that only 80% of purified TNF-BP begins with Asp-41 of SEQ ID NO: 4, while a secondary sequence beginning with Leu-30 of SEQ ID NO: 4 was also detected (page 39, lines 26-31). Clearly, the processing of residues 30-40 of SEQ ID NO: 4 *in vivo* is not wholly efficient and/or precise. Thus, TNF-BP purified from human urine is a mixture of at least two polypeptides whose N-terminus differs by 11 amino acids.

As described above, the purification protocol for human urinary TNF-BP described by Applicants is substantially similar to that described by the inventors of the '953 patent (Wallach *et al.*). In fact, Applicants' purification protocol incorporates the purification steps described by Wallach *et al.*, as well as an additional, highly specific purification step. Wallach *et al.* disclose a TNF-BP purification process involving dialysis and concentration of human urine, ion exchange chromatography, and reverse phase HPLC (*see* related U.S. Patent No. 5,981,701, col. 7-10). Similarly, Applicants' purification scheme involved dialysis and concentration of urine, ion exchange chromatography, and reverse phase FPLC (pages 36-38). Applicants, however, further purified TNF-BP by carrying out an additional, highly specific purification step of affinity chromatography using rTNF (page 36-37). Since Applicants teach an even more extensive purification scheme of TNF-BP than Wallach *et al.*, the preparation of TNF-BP by Wallach *et al.* almost certainly contained the contaminating, uncleaved species of TNF beginning with Leu-30 of SEQ ID NO: 4. Indeed, Wallach *et al.* conceded that his preparation was "substantially purified" and that the "initial yield" from protein micro-sequence analysis was "over 40%, indicating that the major protein in the preparation (the 27 kDa band) is related to the resulting sequence" (*see* related U.S. Patent No. 5,981,701, col. 10, lines 6 and 17-20). Recombinant TNF-BP is not produced via processing of its N-terminus and will not contain contaminants beginning with Leu-30 of SEQ ID NO: 4. Applicants contend, therefore, that the polypeptide encoded by the nucleic acid molecules recited in claims 27, 49, or 67 would differ from the soluble TNF-BP preparation described in the '953 patent.

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Because the '953 patent fails to disclose any information concerning the amino acid sequence of SEQ ID NO: 4, or any information concerning the nucleotide sequence encoding this amino acid sequence (*i.e.*, SEQ ID NO: 3), this reference cannot anticipate an isolated nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO: 3, or an isolated nucleic acid molecule encoding a polypeptide comprising (or consisting of) the amino acid sequence as set forth in SEQ ID NO: 4. Applicants contend, therefore, that the '953 patent cannot anticipate the claimed nucleic acid molecules of the present application, and respectfully request that the rejection of claims 27, 49, 64, 67, 68, 71-74, 76, 77, 79, 81-86, 89-91, 94, 96, 97, 102, 104, 105, 110, 111, 114-116, 119, 121-123, 126, 128-135, 138, 139, 144-168, 170, 172, and 174-178 on 35 U.S.C. § 102 grounds be withdrawn.

6. Rejections of claims 147 and 164 under 35 U.S.C. § 103(a)

The Office Action asserts a rejection of claims 147 and 164 under 35 U.S.C. § 103(a), as being unpatentable over the '953 patent, in view of U.S. Patent No. 4,847,325 (the '325 patent). The Action states that the '325 patent discloses that proteins can be conjugated to a water-soluble polymer, resulting in a biologically active protein having increased circulating half-life in mammals as compared to the unconjugated protein. The Action asserts, therefore, that it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to chemically derivatize the TNF-BP disclosed in the '953 patent with a compound such as PEG, since the '325 patent discloses that the half-life of the protein would be increased *in vivo*.

As described in section 5 above, because the '953 patent does not disclose the complete nucleotide and amino acid sequence of TNF-BP – and in fact, discloses ***only*** fourteen of the first sixteen amino acid residues of a TNF-BP – this reference ***cannot*** anticipate an isolated nucleic acid molecule comprising the nucleotide sequence of SEQ ID NO: 3, or encoding a polypeptide comprising (or consisting of) the amino acid sequence as set forth in SEQ ID NO: 4. As a result of the inadequacy of its disclosure, the '953 patent fails to put a nucleic acid molecule encoding a TNF-BP into the public's possession. Because the disclosure of the '325 patent does not compensate for the shortcomings in the '953 patent, Applicants respectfully request that the rejection of claims 147 and 164 under 35 U.S.C. § 103(a) be withdrawn

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CONCLUSIONS

Applicants respectfully contend that all conditions of patentability are met in the pending claims as amended. Allowance of the claims is thereby respectfully solicited.

If Examiner O'Hara believes it to be helpful, she is invited to contact the undersigned representative by telephone at 312-913-0001.

Respectfully submitted,
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Dated: August 30, 2006

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